REMARKS

Claims 61-63, 65-68, 77, 79-81, 86, 87, 91, 93-101 and 104-115 were pending. Claims 96-100 were previously withdrawn. Claims 61, 67, 77, 86, 104-106, 110, 114 and 115 have been amended.

Support for "*Streptococcus mutans*" in claim 61 can be found in the claims as originally filed and at least, for example, at pages 52-53 and Tables 8 and 9. Accordingly, no new matter has been added to the application by way of these amendments. Support for new claim 116 can be found at least, for example, at page 25.

The foregoing claim amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the present claims prior to being amended herein in this application or in another related application.

In view of the foregoing claim amendments and the arguments set forth below, Applicants respectfully submit that the claims are now in condition for allowance.

Objections to the Claims

The objection to claim 67 at page 4 of the Office Action has been addressed by way of amendment, thereby obviating the objections. Applicants respectfully submit that claim 67 is a proper dependent claim under 37 CFR 1.75 (c), as it includes every limitation of the claim from which it depends, *i.e.,* claim 61, and further limits the characteristics of the bacteria.

The Pending Claims

In some embodiments, pending claims are directed to a composition comprising an amount of a monoclonal antibody effective to prevent staphylococcal infection in neonates and a pharmaceutically acceptable carrier, wherein the antibody specifically binds to poly-glycerol phosphate of Lipoteichoic acid (LTA) of Gram positive bacteria and is of the IgG isotype, wherein the antibody binds to and enhances opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells with or without complement as compared to an appropriate control in an in vitro opsonization assay.

In other embodiments, pending claims are further directed to a composition comprising a monoclonal antibody which specifically binds to poly-glycerol phosphate of LTA of Gram positive bacteria, or antigen binding fragment thereof, and a pharmaceutically acceptable carrier, wherein the monoclonal antibody comprises the complementarity determining regions (CDRs) of the heavy and light chain variable regions of monoclonal antibody 96-110 set forth as SEQ ID NO:87 and SEQ ID NO:89. A composition comprising a monoclonal antibody which specifically binds to poly-glycerol phosphate of LTA of Gram positive bacteria, or antigen binding fragment thereof, and a pharmaceutically acceptable carrier, wherein the monoclonal antibody comprises the heavy chain variable region set forth as SEQ ID NO:87.

Additionally, the pending claims are directed to a composition comprising a monoclonal antibody which specifically binds to poly-glycerol phosphate of LTA of Gram positive bacteria, or antigen binding fragment thereof, and a pharmaceutically acceptable carrier, wherein the monoclonal antibody comprises the light chain variable region set forth as SEQ ID NO:89.

The pending claims are also directed to a composition comprising a monoclonal antibody of claim 61, wherein the monoclonal antibody comprises a heavy chain comprising the heavy chain complementarity determining regions (CDRs) of the monoclonal antibody 96-110 and a variable region having 80% amino acid identity with SEQ ID NO:87.

The pending claims are also directed to a composition comprising a monoclonal antibody of claim 61, wherein the monoclonal antibody comprises a light chain comprising the light chain complementarity determining regions (CDRs) of the monoclonal antibody 96-110 and a variable region having 80% amino acid identity with SEQ ID NO:89.

The pending claims are also directed to a composition comprising a monoclonal antibody of claim 61, wherein the monoclonal antibody comprises a heavy chain comprising the complementarity determining regions (CDRs) of the monoclonal antibody 96-110 heavy chain variable region set forth as SEQ ID NO:87 and having at least 70% amino acid identity with the monoclonal antibody 96-110 heavy chain variable region set forth as SEQ ID NO:87.

The pending claims are also directed to a composition comprising a monoclonal antibody of claim 61, wherein the monoclonal antibody comprises a light chain comprising the complementarity determining regions (CDRs) of the monoclonal antibody 96-110 light chain variable region set forth as SEQ ID NO:89 and having at least 70% amino acid identity with the monoclonal antibody 96-110 light chain variable region set forth as SEQ ID NO:89.

Rejection of Claims 61, 77, 79-81, 86-87, 93, 95, 101 and 104-115 Under Doctrine of Obviousness-type Double Patenting

The Examiner has maintained the rejection of claims 61, 77, 79, 93 and 95 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-7, 9-12 and 14-19 of U.S. Patent No. 6,610,293. The Examiner has also rejected claims 61, 101 and 104-115 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-6, 9-12 and 14-19 of U.S. Patent No. 6,610,293. Applicants will consider filing a terminal disclaimer over the 6,610,293 patent when the remaining rejections have been overcome.

The Examiner has maintained the provisional rejection of claims 77, 81, 86-87 and 93 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 53-58 and 79-83 of copending Application No. 11/193,440. The Examiner has also provisionally rejected claims 104-115 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 53, 83, 91-92 and 96 of copending Application No. 11/193,440. This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. If appropriate, Applicants will address any obviousness-type double patenting issues upon an indication of allowance of claims in Application No. 11/193,440 or in the instant application.

The Examiner has also maintained the provisional rejection of claims 77, 79-81, 86-87 and 93 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40-43, 47-68 and 72 of copending Application No. 10/323,926. This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. If appropriate, Applicants will address any obviousness-type double patenting issues upon an indication of allowance of claims in Application No. 10/323,926 or in the instant application.

Rejection of Claims 61-63, 65-68, 77, 79-81 86, 87, 91, 93-95, 101 107-109 and 104-115 Under Section 112, First Paragraph

The Examiner has rejected claims 61-63, 65-68, 77, 79-81 86, 87, 91, 93-95, 101 and 104-115 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement as allegedly comprising new matter for recitation of the phrase "binding affinity of about 10^{-8} M." Without acquiescing and solely in the interest of expediting prosecution,

recitation of the phrase "binding affinity of about 10^{-8} M" has been deleted, thus rendering the rejection moot.

The Examiner has also rejected claims 107-109 and 111-115 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description for allegedly being drawn to a vast genus of variable regions of amino acids of SEQ ID NO:87 and SEQ ID NO:89. wherein the variable region has 70%, 85%, 90% and 95% amino acid identity with SEQ ID NO:87 and SEQ ID NO:89.

Without acquiescing and solely in the interest of expediting prosecution, claims 106,110, 114, and 115 have been amended to depend from claim 61.

Rejection of Claims 61 and 86
Under Section 112, Second Paragraph

Claims 61 and 86 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to distinctly claim the subject matter which applicant regards as the invention.

Claim 61 has been rejected for the recitation of the phrase "binding affinity of about." Without acquiescing and solely in the interest of expediting prosecution, claim 61 has been amended to delete recitation of "about," thus obviating the rejection.

Claim 86 has been rejected as being dependent from a cancelled claim. Claim 86 has been amended, thus obviating the rejection.

Rejection of Claims 61, 62, 65-67, 81, 86, 87 and 93
Under Section 102(b)

The Examiner has maintained rejection of claims 61, 62, 65-67, 81, 86, 87 and 93 under §102(b) as being anticipated by Hamada *et al.* in light of Roitt *et al.* This rejection is respectfully traversed.

The subject matter of the pending claims is set forth above. The Examiner states that the 3G6 antibody disclosed by Hamada *et al.* would inherently opsonize gram positive bacteria in light of the teaching of Roitt. The Examiner relies on Roitt as teaching that "antibodies inherently have the ability to opsonize bacteria by virtue of their binding...to a large extent as compare [sic] to the absence of any opsonin (see page 16 of the Office Action dated February 23, 2007). The Examiner further states that Kaufmann *et al.* teach that bacteria possess a polysaccharide capsule, "which is in itself antiphagocytic, preventing uptake by host cells." The Examiner relies on Kaufmann *et al.* for the proposition that "if bacteria is not opsonize [sic] it

could be because a polysaccharide capsule is antiphagocytic." The Examiner concludes that "a monoclonal antibody that binds to lipoteichoic acid ***may*** not opsonize for the reason listed above and not because a monoclonal antibody bound to lipoteichoic acid is not capable." (emphasis added).

Under principles of inherency, "if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates [the claim]." *Mehl/Biophile Int'l Corp. v. Milagraum,*192 F.3d 1362, 1365 (Fed Cir. 1999). To show that the prior art "necessarily" functions in accordance with, or includes the claimed limitations, one must show more than a mere probability or possibility of the inherent feature's existence. *See SmithKline Beecham Corp. v. Apotex Inc.,* 403 F.3d 1331, 1346 (Fed. Cir. 2005). Therefore, "[i]nherency...***may not be established by probabilities or possibilities***. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Mehl/Biophile,* 192 F.3d 1362 at 1365 (emphasis added) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (CCPA 1939)).

Applicants respectfully submit that the data and literature support that it is the properties of an antibody itself that determine whether an antibody is opsonic and that the prior art antibodies do not have the properties set forth in the pending claims. Applicants' arguments are set forth below.

I. Antibodies Can Mediate Opsonization - Even of Polysaccharide Encapsulated Bacteria

Bacteria can be engulfed and killed by phagocytic cells in a subject. However, this process can be inefficient, particularly if the bacteria comprise a capsule. Polysaccharide capsules can help bacterial cells evade phagocytosis. However, phagocytosis of bacteria, ***with or without a capsule***, can be enhanced by antibody molecules. Bacteria are bound by the antigen binding sites of opsonic antibodies and the Fc portions of these opsonic antibodies bind to Fc receptors on phagocytes, such as neutrophils and macrophages. By this mechanism, opsonic antibodies facilitate the interaction of encapsulated or non-encapsulated bacteria with phagocytes and their subsequent engulfment by those phagocoytes (Immunology- A short Course (Benjamini et al.), the relevant portion of which is attached hereto as Appendix E and Bacterial Pathogenesis- A Molecular Approach, Salyers and Whitt, Chapter 8, the relevant portion of which is attached hereto as Appendix F). Thus, in contrast to the Examiner's assertion, polysaccharide capsules are not antiphagocytic when antibodies are present.

II. Only Opsonic Antibodies Are Protective Against Neonatal Staphylococcal Infections; Binding To The Target Is Not Sufficient

The antibodies presently claimed are administered to subjects, e.g., neonates, to prevent infection with Staphylococci. Because these antibodies are used in passive immunization protocols, the Examiner's comments regarding the induction of immune responses by bacteria are not relevant. Applicants provide data which shows that the claimed antibodies can enhance survival in an animal model of lethal coagulase positive and coagulase negative staphylococcal infections. This enhancement occurred in an adult animal model and an immunocompromised animal model (immature neonatal immune system). The critical factor in enhancing survival in a subject is that the antibody is opsonic. Opsonic activity of an antibody is predictive of the ability of an antibody to confer protection against bacterial infection (see *e.g.,* Henckaerts *et al.,* Vaccine. 2007 Mar 22;25(13):2518-27, attached hereto as Appendix G). Further, this is the standard and definition currently accepted by the FDA.

Moreover, it is known in the art that mere concentration of antibody is not sufficient to provide protection, *i.e.,* opsonize bacteria (see Clark and Easmon, J Clin Pathol. 1986 Aug;39(8):856-60, attached hereto as Appendix H). Specifically, Clark and Easmon show that 14 different intravenous immunoglobulin (IVIG) lots tested for opsonic activity against *S. epidermidis* differ despite comparable levels of immunoglobulin concentrations between the lots, thus showing that high concentrations of antibody do not correlate with the ability of an antibody to be opsonic.

Antibodies must be tested for their ability to opsonize bacteria and, as presented in more detail below, not all anti-LTA antibodies are opsonic.

III. Not All Anti-LTA Antibodies Are Opsonic

As described in a recent review article, whether or not antibodies are opsonic may be determined by the nature of the underlyting T cell response to an antigen. (Seder et al. 2008. Nature Reviews/ Immunology 8:247, attached hereto as Appendix I). For example as stated in Seder et al., T helper cells can be divided into two functional subsets:

> [f]unctional subsets of CD4+ T cells expression the αβ-T-cell receptor that produce either type-1 cytokines (IL-2, IFNγ and other cytokines that support macrophage activation, the generation of cytotoxic T cells ***and the production of opsonizing antibodies***), or type-2 cytokines (IL-4, IL-5, IL-13 and other cytokines that support B-cell activation, ***production of non-opsonizing antibodies***, allergic reactions and expulsion of extracellular parasites). See page 248, leftmost column, second paragraph.

Thus, the cytokine milieu which develops during the course of an immune response can influence whether antibodies that are made are opsonic or not and, thus, not all immune responses lead to the generation of opsonic antibodies.

With respect to LTA specifically, Applicants have developed a number of anti-LTA antibodies and they are not all inherently opsonic, even when tested against the same strain of bacteria as illustrated by the table in Appendix A.

As shown in the table, antibodies 1-5 opsonize *S. epidermidis* strain 1175, while antibodies 6 and 7 do not. Antibodies 1-3 opsonize strain 4555, while the other anti-LTA antibodies do not. These data indicate that not all antibodies are opsonic, even against the same bacterial strains.

Thus, the Examiner's assertion that antibodies inherently have the ability to opsonize bacteria by virtue of their binding to FcR is incorrect and does not address the fact that some antibodies do not have the ability to opsonize bacteria even though they bind to FcR.

IV. The Antibody Taught by Hamada is Different From the Antibodies Presently Claimed

The pending claims are directed to opsonic antibodies having particular characteristics:

A composition comprising an amount of a monoclonal antibody effective to prevent staphylococcal infection in neonates and a pharmaceutically acceptable carrier, wherein the antibody specifically binds to poly-glycerol phosphate of Lipoteichoic acid (LTA) of Gram positive bacteria and is of the IgG isotype, wherein the antibody binds to and enhances opsonization of multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans* by phagocytic cells with or without complement as compared to an appropriate control in an in vitro opsonization assay.

A. There is no teaching or suggestion in the Hamada reference that the 3G6 antibody is opsonic; the agglutination data presented indicate that the 3G6 antibody is not of a high avidity and would not be opsonic.

As set forth above, simple binding to an isolated antigen is not predictive of opsonization (see Table 1 above). The ELISA data presented in Hamada shows that the 3G6 antibody binds a number of organisms. This ELISA data is based on binding to intact bacterial cells. Thus, these data are based on binding to complex antigens that comprise many representations of a single epitope and, thus, would encourage binding of low affinity antibodies. In contrast to the ability to merely bind bacteria, the agglutination or opsonization of bacterial cells requires binding to multiple points on the organism. Such multi-point binding requires that antibodies be of high avidity.

The Hamada reference provides agglutination data which shows that the 3G6 antibody can agglutinate only two of the *S. epidermidis* strains tested and not *S. aureus*; no opsonization data is presented. The fact that the 3G6 Hamada antibody could not agglutinate all of the organisms tested indicates that the 3G6 antibody, while it may be capable of the single-point attachment necessary to bind to LTA present on bacteria, is not of high enough avidity to achieve the multi-point binding required to agglutinate bacterial cells. In contrast, the presently claimed opsonic antibodies are of high avidity. In fact, the opsonic antibodies of the invention are of sufficient avidity to inhibit the interaction between LTA and its receptor, toll-like receptor 2, on phagocytic cells, e.g., macrophages and neutrophils. The claimed opsonic antibodies facilitate multi-point interaction with isolated LTA or LTA expressed on bacterial cells and competitively inhibit the interaction of LTA with toll-like receptor 2 (see Appendix B). The figure in Appendix B shows that the claimed antibody blocks the binding of LTA to toll-like receptor 2 with sufficient avidity to reduce LTA-mediated cytokine production.

The data in Hamada showing a lack of agglutination of all of the organisms required by the pending claims indicates the 3G6 antibody would not bind with a sufficiently high avidity to the recited organisms to effectively competitively inhibit the binding of LTA to its cellular receptor and, thus, would not inhibit cytokine formation. Given this demonstrated lack of high avidity binding, the 3G6 antibody would not be expected to be opsonic.

B. The 3G6 antibody is not appropriate for therapeutic use.

In addition, the fact that the data presented in Hamada show binding of 3G6 to whole organisms, but not agglutination of the organisms, indicates that the antibody would be neither opsonic nor would it inhibit inflammation induced by LTA. Importantly, the heterogeneity in functional activity (agglutination) displayed by the 3G6 antibody clearly indicates that the antibody is not appropriate for therapeutic use, *e.g.*, for preventing staphylococcal infections in neonates, as required by the claims. A key property for an antibody that is appropriate for use in preventing Staphylococcal infection is that the antibody be capable of opsonizing both *S. epidermidis* and *S. aureus*. As many different strains of staphylococcal organisms have been found to be present in nearly every neonatal subject tested in the clinic, the ability of an antibody to opsonize multiple serotypes of *Staphylococcus epidermidis,* coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus mutans,* and not just some, is critical. As set forth above, the 3G6 antibody of Hamada only agglutinates two of the *S. epidermidis* strains tested and *not S. aureus*. The fact that the 3G6 antibody only shows functional binding to *some* whole bacterial cells means that it would not be therapeutically effective. Therefore, it is not a useful clinical reagent. In fact, the authors themselves only conclude that the 3G6 antibody would be useful in ***diagnostics***[1]***;*** there is no indication in the reference that the antibody would be clinically useful.

In contrast to the 3G6 antibody described in Hamada *et al.,* the claimed antibodies not only prevent infection with *S. epidermidis* and *S. aureus* in neonates, but work on both organisms at roughly equivalent concentrations (see Appendix C). Figure 1 in Appendix C shows that antibodies having the claimed characteristics, at a concentration of 60 mg/kg, provide protection against *S. aureus* in a suckling rat. Figure 2 in Appendix C shows that antibodies having the claimed characteristics provide protection against *S. epidermidis* in a suckling rat at 40 and 80 mg/kg. Thus, in contrast to the 3G6 antibody, the data shown in Appendix C show that antibodies having the claimed characteristics not only provide protection against ***both*** *S. aureus* and *S. epidermidis* but do so at ***equivalent*** concentrations. Furthermore, the inventors have shown that antibodies having the claimed characteristics opsonize 26 different isolates of

[1] See page 1020 of Hamada *et al.,* "3G6 mAb will prove to be an invaluable tool in investigations regarding the role of LTAs in lymphocyte activation…"

coagulase negative staphylococci tested (CoNS) (see Appendix D). This consistency is critical in for prevention of infection and is not demonstrated by the 3G6 antibody.

In addition, the Hamada *et al.* reference fails to teach or suggest a composition comprising an amount of a monoclonal antibody ***effective to prevent staphylococcal infection in neonates.*** The Hamada *et al.* reference also fails to teach or suggest a monoclonal antibody having the structural properties required by claim 77, the claims that depend therefrom, and claims 104-115.

In view of all of the foregoing, the Hamada *et al.* reference cannot be found to inherently anticipate the presently claimed invention with certainty. Therefore, applicants respectfully request that the rejection under 35 U.S.C. §102(b) be reconsidered and withdrawn.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: September 9, 2008

Respectfully submitted,

By /Megan E. Williams/
Electronic Signature for Megan E. Williams, Ph.D.
Registration No.: 43,270
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant

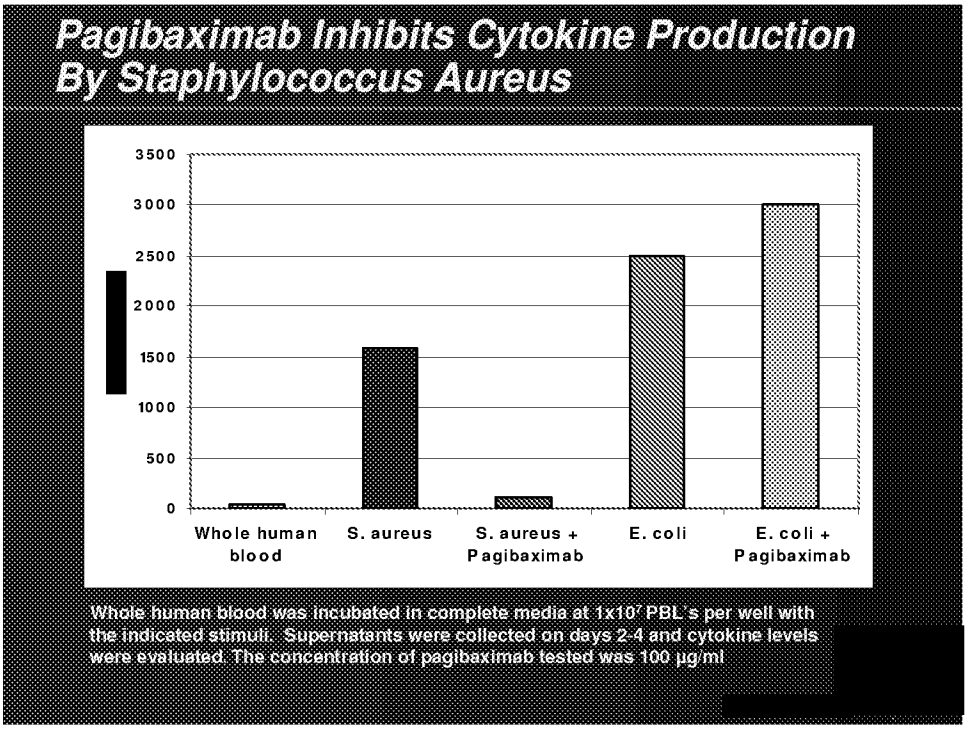
APPENDIX A

Table 1. Anti-LTA Opsonization Data

Antibody ID Code	Target	Antibody Concentration (ug/ml)	% opsonized S. epidermidis Strain 1175	% opsonized S. epidermidis Strain 4555	n	Experiment
1	LTA	200	96	42	2	02-62; 02-63
		10	91.5	0	2	02-62; 02-63
2	LTA	200	91	0	1	02-63
		10	97	36	1	02-63
3	LTA	200				
		10	100	20	1	02-63
4	LTA	200	54	0	1	02-62
		10	55	0	1	02-62
5	LTA	200	60	0	1	02-63
		10	76	0	1	02-63
6	LTA	200				
		10	0	0	1	02-62
7	LTA	200				
		10	0	0	1	02-62

* 2 is a chimeric antibody containing the V regions of antibody 1, but with two amino acid changes in the Fc that render the antibody unable to be bound by Protein A from *S. aureus*.

APPENDIX B


Pagibaximab Inhibits Cytokine Production By Staphylococcus Aureus
3500
3000
2500
2000
1500
1000
500
0
Whole human blood
S. aureus
S. aureus + Pagibaximab
E. coli
E. coli + Pagibaximab
Whole human blood was incubated in complete media at 1x10⁷ PBL's per well with the indicated stimuli. Supernatants were collected on days 2-4 and cytokine levels were evaluated. The concentration of pagibaximab tested was 100 µg/ml

APPENDIX C

Figure 1

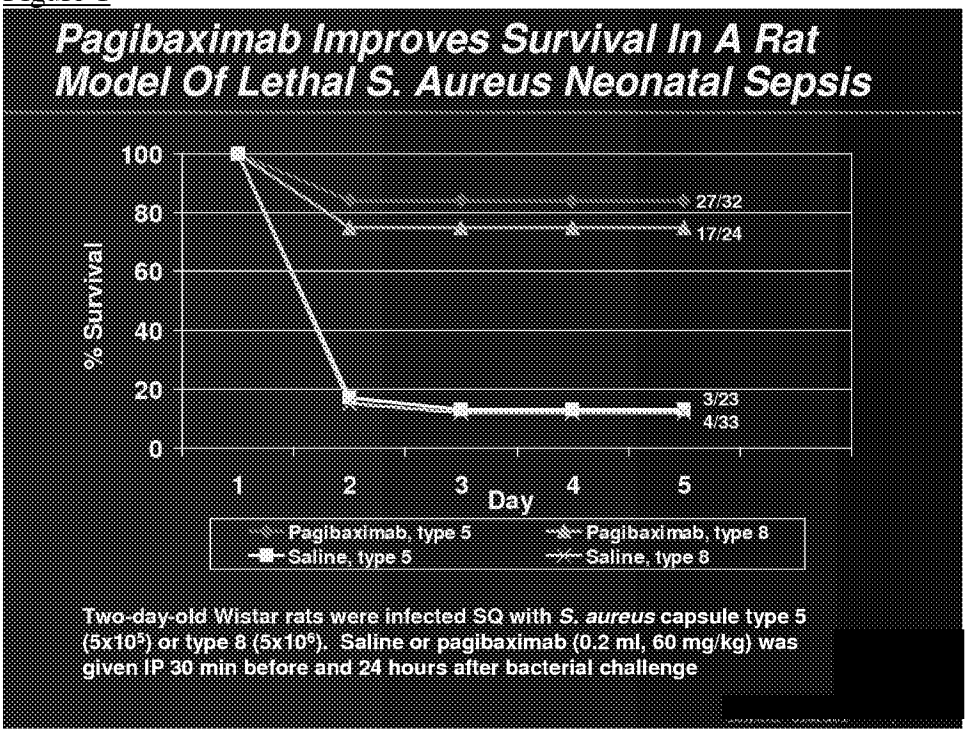
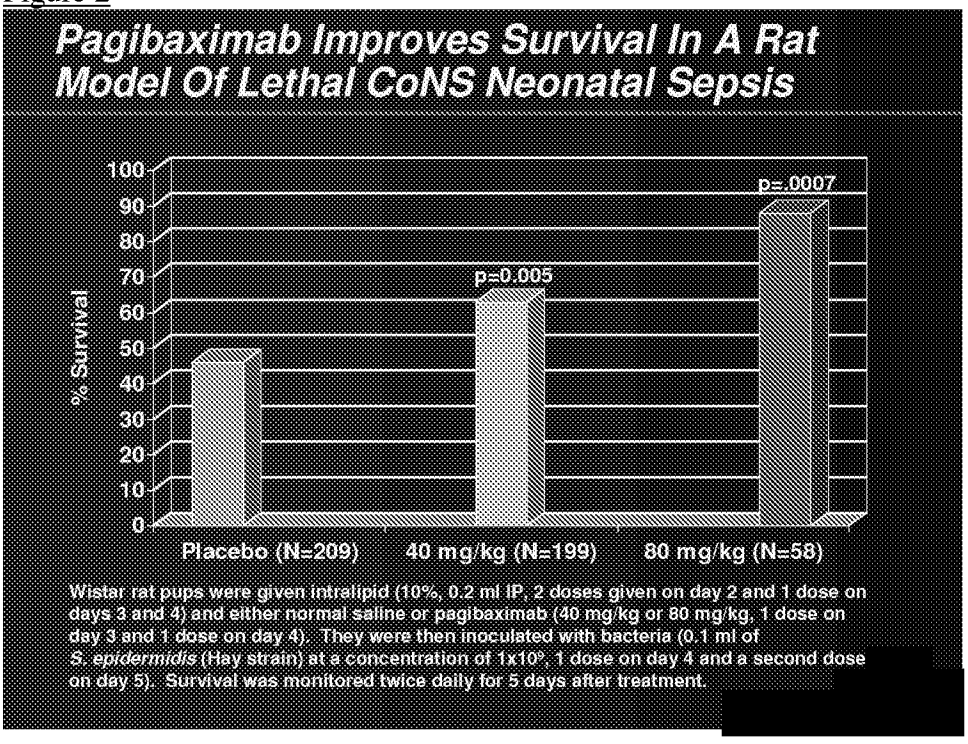
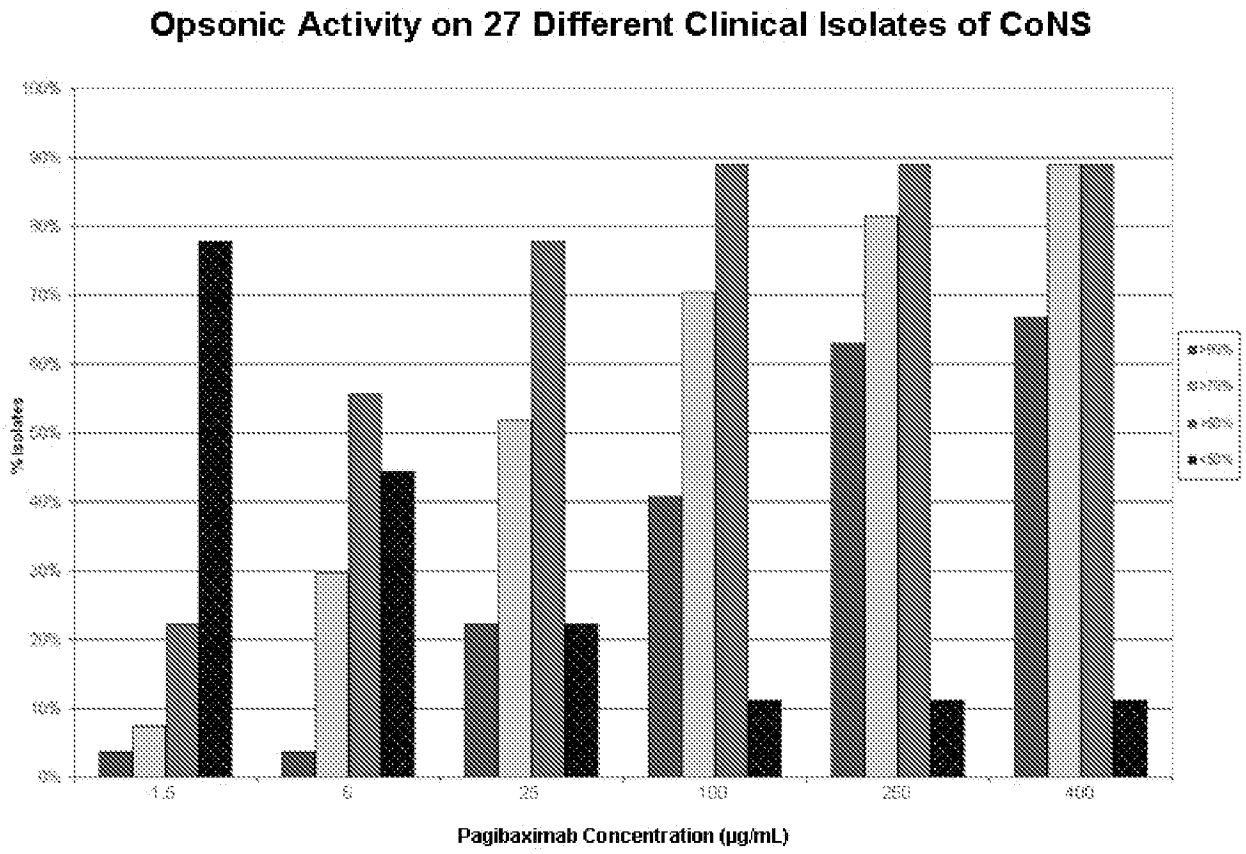


Figure 2



APPENDIX D


Opsonic Activity on 27 Different Clinical Isolates of CoNS
% Isolates
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1.5
6
25
100
250
400
Pagibaximab Concentration (µg/mL)